UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/752,659	01/07/2004	Marc Elliot Rothenberg	CMC-161	4105

26875 7590 10/31/2007
WOOD, HERRON & EVANS, LLP
2700 CAREW TOWER
441 VINE STREET
CINCINNATI, OH 45202

EXAMINER	
HISSONG, BRUCE D	
ART UNIT	**PAPER NUMBER**
1646	

MAIL DATE	DELIVERY MODE
10/31/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/752,659	ROTHENBERG ET AL.	
	Examiner	Art Unit	
	Bruce D. Hissong, Ph.D.	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on 4/28/2006.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1, 3, 5-14, 16-21, 23-34, 44-45, and 47-49 is/are pending in the application.

4a) Of the above claim(s) 8,12 and 30 is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1,3,5-7,9-11,13,14,16-21,23-29,31-34,44,45 and 47-49 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Formal Matters

1. Applicants response to the office action mailed on 1/31/2006, including arguments/remarks and amended claims, was received on 4/28/2006 and has been entered into the record.

2. In the Applicants' response, claims 2, 4, 15, 22, 35-43, 46, and 50 were cancelled. Therefore, claims 1, 3, 5-14, 16-21, 23-34, 44-45, and 47-49 are currently pending.

3. In the response received on 4/28/2006, the Applicants requested that withdrawn claim 8 be reinstated because Applicants elected "lung" as the location of transmigration, which is recited in claim 8. It is noted, however, the Applicants elected "receptor internalization" as the species of eosinophil function. Claim 8, which is drawn to the eosinophil function of transmigration, rather than receptor internalization, thus remains withdrawn.

4. Therefore, claims 8, 12, and 30 are withdrawn as non-elected subject matter, and claims 1, 3, 5-7, 9-11, 13-14, 16-21, 23-29, 31-34, 44-45, and 47-49 are the subject of this office action.

Claim Objections

1. Claims 1, 3, 5-7, 9-11, 13-14, 16-21, 23-29, 31-33, 44-45, and 47-49 are objected to for reciting non-elected subject matter, as originally applied to claims 1, 3, 9-10, 16, 20, 29, 32-33, and 48 on page 2 of the office action mailed on 1/31/2006. Due to the Applicants' election of Group I, drawn to methods of administering MIG to inhibit eosinophil recruitment or function, the recitation of administration of IP-10 represents a recitation of non-elected subject matter.

2. The Examiner suggests the syntax of claim 1 can be improved by amending the claim to read on a method of "administering a pharmaceutical composition comprising an isolated cytokine.....wherein said cytokine exhibits eosinophil recruitment- or function-inhibitory activity, in a pharmaceutically effective amount....", or something similar. As written, the claim can be interpreted as reading on a pharmaceutical composition comprising a cytokine, wherein said cytokine inhibits

eosinophil recruitment or function, or alternatively, a pharmaceutical composition comprising an isolating cytokine and also comprising eosinophil recruitment- or function-inhibiting activity". Additionally, claims 3, and 5-7 are objected to as depending from objected claim 1.

3. Similarly, the Examiner suggests amending claim 44 to recite administering to a patient "a pharmaceutically acceptable formulation of a cytokine.....wherein said cytokine substantially lacks eosinohil chemoattraction activity and inhibits at least one of eosinophil chemoattraction or eosinophil activation.", or something similar.

4. The Examiner suggests amending claim 10 to recite the method of claim 9 wherein eosinophilia is reduced "in the lung" or "in a lung".

5. Claim 45 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. In the instant case, independent claim 44 recites a method of administering a specific cytokines, MIG or IP-10, whereas dependent claim reads on administering any Th1 cytokine.

6. The Examiner suggests amending claim 44 from "negatively affecting at least one of eosinophil chemoattraction or eosinophil activation activity" to "inhibiting eosinophil chemoattraction and/or activation."

7. Claims 3 and 5 are objected to for depending from base claims rejected under 35 U.S.C. 102(b) (see 35 U.S.C. 102(b) rejections 2 and 3 below).

8. The Examiner suggests amending claim 49 from "Th1 associated" and "eosinophil associated" to "Th1-associated" and "esosinophil-associated", respectively.

Claim Rejections - 35 USC § 112, first paragraph - enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Rejections withdrawn

1. Rejection of claims 1, 7, 21, 23, 27-28, 44-45, and 47-49 under 35 USC § 112, first paragraph, regarding lack of enablement for methods of administering any cytokine other than MIG or IP-10, as set forth on pages 2-6 of the prior office action mailed on 1/31/2006, is *withdrawn* in response to Applicants' amendments to the claims to recite administration of pharmaceutical compositions comprising a cytokine selected from the group consisting of MIG or IP-10.

Rejections maintained

2. Claims 3 and 14 and 16-20 *remain rejected* under 35 USC § 112, first paragraph, regarding lack of enablement for methods of inhibiting eosinophil recruitment or function by administration of any peptide derived from MIG or IP-10, and methods of inhibiting an eosinophil response to any chemoattractant other than eotaxin-1, -2, or –3, as set forth on pages 2-6 of the prior office action mailed on 1/31/2006.

In the Applicants response received on 4/28/2006, the Applicants state that the rejection under 35 USC 112, first paragraph, is overcome with respect to cancelled claim 4, and improperly applied to original claims 1-3, 5-7, 14-23, 27-28, and 44-50, but do not set forth any specific reasons as to why the rejection was improperly applied.

It is noted that the rejection of claims 1, 7, 14, 16, 17-21, 23, 27-28, 44-45, and 47-49 was overcome by the Applicants' amendments to the claims, as discussed *supra*. However, claim 3 is still drawn to administration of a peptide derived from MIG or IP-10. The specification does not teach any MIG- or IP-10-derived peptides that can function as eosinophil activity inhibitors, and also does not provide guidance or examples of how any such peptides could be "derived" from MIG or IP-10. Thus, one of ordinary skill in the art would not be able to predict which of the many possible peptide fragments of MIG or IP-10, or any polypeptides comprising any point mutations such as additions, substitutions, and/or deletions, or any other type of modification resulting in a molecule which can be considered "derived from" MIG or IP-10, would be useful. For these reasons, one of ordinary skill in the art would require further, undue experimentation in order to practice a method of administering any peptide "derived" from either MIG or IP-10.

Furthermore, independent claim 14 reads on a method of treatment comprising administration of MIG or IP-10 in an amount sufficient to inhibit an eosinophil response to a chemoattractant. As written, the claim reads broadly on inhibiting all possible eosinophil responses to all possible chemoattractants. The specification provides guidance and examples showing that MIG administration inhibits eosinphil

chemoattraction in response to eotaxins (eotaxin-1, -2, and –3), but does not provide examples of MIG inhibition of chemoattraction in response to any other chemoattractant. Due to the wide range of molecules that could function as chemoattractants, and the wide variety of diseases or conditions mediated by such chemoattractants, a person of ordinary skill in the art would not predict which of the many possible diseases or conditions mediated by any and all chemoattractants, or any diseases or conditions mediated by any chemoattractants other than eotaxin-1, -2, or –3, other than eosinophil chemoattraction, could be treated by the claimed methods, and therefore a person of ordinary skill in the art would require further, undue experimentation in order to determine which chemoattractants could be inhibited by the claimed method and thus practice the claimed method in a manner commensurate in scope with the claims.

3. Claims 14, 16-20, 27-33, and 49 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods of treating a patient with eosinophilia or allergic conditions including asthma, does not reasonably provide enablement methods of treating all other possible diseases or conditions by administration of a composition comprising MIG. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Independent claims 14 and 27 are drawn to methods of treating a subject, wherein said method comprises administering a pharmaceutical composition comprising MIG. The claims do not recite a specific patient population, or a specific disease to be treated, and thus the breadth of the claims is excessive because the claims read on methods of treating all possible diseases or conditions, in all possible patient populations. Furthermore, claim 29 only requires a patient with eosinophila, and is not drawn to any particular disease. Similarly, claim 49 recites a patient with an "eosionophil associated disease", and does not recite any specific disease or condition. The specification provides guidance and examples showing administration of MIG to eosinophils inhibits eosinophil recruitment and function, and thus suggests that such eosinophil inhibition by MIG would be effective in treating diseases in which eosinophils play a role in promoting inflammation or other allergic reactions. However, there is no guidance or examples showing that any other type of diseases or conditions would be effectively treated by the claimed methods. A person of ordinary skill in the art would not be able to predict how to practice the claimed method for treating diseases in which there is no eosinophil-mediated inflammatory component. For example, the claims read on treatment of eosinophil-mediated diseases, as well as conditions such as heart disease. A person of ordinary skill in the art would not predict that

administration of MIG would have any effect on heart disease, and would require further, undue experimentation in order to practice such a method or any other method of treating any disease not mediated by eosinophils. Therefore, the specification is not enabling for the full breadth of the claims as currently written.

Claim Rejections - 35 USC § 112, first paragraph – written description

Rejections withdrawn

1. Rejection of claims 1, 7, 14, 16, 17-21, 23, 27-28, 44-45, and 47-49 under 35 USC § 112, first paragraph, regarding lack of written description for the genus of cytokines having eosinophil recruitment- or function-inhibiting activity, as set forth on pages 6-8 of the prior office action mailed on 1/31/2006, is *withdrawn* in response to Applicants' amendments to the claims to recite administration of pharmaceutical compositions comprising a cytokine selected from the group consisting of MIG or IP-10, and methods of inhibiting eosinophil responses to eotaxin-1.

Rejections maintained

2. Claim 3 *remains rejected* under 35 USC § 112, first paragraph, regarding lack of written description for the genus of peptides derived from MIG or IP-10, as set forth on pages 6-8 of the prior office action mailed on 1/31/2006.

In the Applicants response received on 4/28/2006, the Applicants state that this rejection is overcome with respect to cancelled claim 4, and improperly applied to original claims 1-3, 5-7, 14-23, 27-28, and 44-50, but do not set forth any specific reasons as to why the rejection was improperly applied. It is noted that the rejection of claims 1, 7, 14, 16, 17-21, 23, 27-28, 44-45, and 47-49 was overcome by the Applicants' amendments to the claims, as discussed *supra*. However, claim 3 is still drawn to a genus of peptides derived from MIG or IP-10 that has not been adequately described in the specification. The specification does not describe any peptides derived from either MIG or IP-10, and furthermore does not describe the sequence or structural elements of either chemokine that must be conserved in order to maintain the desired eosinophil-inhibiting function. Thus, there is no disclosure of any complete or partial structure required of the claimed peptides, nor any physical/chemical properties, functional characteristics, or structure/function correlation that would otherwise provide distinguishing characteristics of the claimed genus. For these reasons, the claimed genus of peptides derived from MIG or IP-10 has not been adequately described in the specification in such a manner as to reasonably convey

to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed genus.

- *New grounds of rejection*

3. Claim 31 is rejected under 35 U.S.C. 112, first paragraph, containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claim is drawn to a method of eosinophil inhibition, wherein recruitment is responsive to a genus of chemokines. The specification provides description of chemokines capable of stimulating chemotaxis, wherein said chemokines are eotaxin-1, -2, and –3, but does not describe in any other chemokine capable of stimulating recruitment, wherein said recruitment can be inhibited by administration of MIG or IP-10.

To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof. In this case, the only factor present in the claims is a requirement that the claimed recruitment be in response to a chemokine. There is no identification of any particular chemokine(s), other than eotaxins, that is capable of mediating the claimed effect. Accordingly, in the absence of sufficient distinguishing characteristics, the specification does not provide adequate written description of the claimed genus.

Claim Rejections - 35 USC § 112, second paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Rejections maintained

1. Claims 6-7 *remain rejected* under 35 USC § 112, second paragraph, as being indefinite regarding the metes and bounds of the phrase "perturbed", as set forth on page 9 of the prior office action mailed on 1/31/2006. In the response received on 4/28/2006, the Applicants do not address this rejection, and therefore this rejection is maintained for reasons of record. It is also noted, that the term "perturbed"

can encompass any qualitative or quantitative change in any signal transduction kinase function, and specifically any change in Erk-1 or –2 activity or function. Furthermore, the claims do not state the nature of any perturbation of Erk (physical change, chemical/biochemical change, difference in activity, etc?), and also do not set forth any specific signal transduction kinase function which can be perturbed.

2. Claim 27 *remains rejected* under 35 USC § 112, second paragraph, as being indefinite regarding the metes and bounds of the phrase "cytokine capable of negatively regulating an inflammatory cell within a lung", as set forth on page 9 of the prior office action mailed on 1/31/2006.

In the response received on 4/28/2006, the Applicants argue that one skilled in the art would appreciate that a cytokine "negatively regulating" an inflammatory cell down-regulates the inflammatory cell's intrinsic ability to provide a pro-inflammatory response, which could be determined, for example, by measuring the reduction in its secretion of pro-inflammatory agents, its cell-cell contact, its activation of other cells in a pro-inflammatory cascade, etc.

These arguments have been fully considered and are not persuasive. The claims do not set forth any specific function or activity that can must be negatively regulated, or define any degree to which a cell may be negatively regulated. As written, the claim reads on regulation, to any degree, of any activity, function, or property of a cell. The claim also does not specify any standard or control as to which to determine if a cell has been regulated in a negative manner, and therefore the claim is indefinite in regards to this limitation.

3. Claim 44 *remains rejected*, and dependent claims 45 and 47-48 are also rejected under 35 USC § 112, second paragraph, as being indefinite regarding the metes and bounds of the phrase "negatively effecting at least one of eosinophil chemoattraction or eosinophil activation activity", as set forth on page 9 of the prior office action mailed on 1/31/2006.

In the response received on 4/28/2006, the Applicants argue that one skilled in the art would know that "negatively affecting" is a decrease or inhibition, in quantity and/or quality, of chemoattraction or activation in the presence of the cytokine, and thus the metes and bounds of the claim can be determined by quantitative or qualitative chemoattraction or activation assays in the presence, versus the absence, of said cytokine.

These arguments have been fully considered and are not persuasive. Claim 44 recites negatively affecting eosinophil activation activity. Given the broadest reasonable interpretation, "eosinophil activation activity" could be any activity that results in eosinophil activation, or any activity that results

from eosinophil activation. It is not clear which of the many possible eosinophil activation activities are to be negatively affected by the claimed method, and therefore the metes and bounds of "negatively affecting" "eosinophil activation activity" has not been described in the claims or the specification.

4. Claims 47-48 *remain rejected* under 35 USC § 112, second paragraph, as being indefinite regarding the metes and bounds of the phrase "negatively effected" in relation to a Th2 cytokine (claim 47) or eotaxin-1 (claim 48), as set forth on page 9 of the office action mailed on 1/31/2006.

In the response received on 4/28/2006, the Applicants argue that "negatively affected" is a decrease or inhibition in quantity and/or qualitative function in eotaxin-1 in the presence of the cytokine. Thus, the metes and bounds of the term can be determined by quantitative or qualitative eotaxin-1 assays in the presence, versus the absence, of said cytokine.

These arguments have been fully considered and are not persuasive. The claims do not define the nature of any negative effect of said cytokine, or recite any specific activity or function that is to be negatively affected. Although a person of skill in the art would likely be able to determine if the function of a Th2 cytokine, or eotaxin-1, was inhibited by MIG, the claims do not actually require this limitation. Given the broadest reasonable interpretation, negatively affecting any Th2 cytokine, or eotaxin-1, could be inhibiting a known function of said cytokine/eotaxin-1, or a physical alteration to said cytokine/eotaxin-1 that impacts said cytokine/eotaxin-1 in a "negative" manner. For example, altering the net charge of a cytokine or eotaxin-1 may have a "negative" effect *in vitro* when conducting electrophoretic assays. Thus, because the metes and bounds of "negatively affecting" has not been described in the claims or the specification, the claims are indefinite.

New Grounds of Rejection

5. Claim 31 recites the limitation "recruitment" in the method of claim 29. There is insufficient antecedent basis for this limitation in the claim.

6. Claim 49 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The claim recites the limitation "eosinophil associated diseases". The intended meaning of this term is not defined by the claims or the specification. The metes and bounds of what diseases are diseases are considered to be "associated with" are not defined. Furthermore, the metes and bounds of the term "associated" is also not clear because the nature of the association is not defined.

7. Claims 14, 15-20, 27-28, and 49 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential elements, such omission amounting to a gap between the elements. See MPEP § 2172.01. Independent claims 14, 27, and 49 are drawn to methods of treatment comprising administration of MIG or IP-10. However, the claims do not define or recite an intended patient population, or a population of individuals requiring treatment with said methods. The omitted elements are: therefore a recitation of intended patient populations.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Rejections withdrawn

1. Rejection of claims 1, 3, 9-11, 13-14, 16-21, 23-29, 31-33, 44-45, and 47-49 under 35 USC § 102(b) as being anticipated by Kuna et al ("Kuna" – WO 94/21277), as set forth on pages 9-11 of the office action mailed on 1/31/2006, is *withdrawn*.

In the response received on 4/28/2006, the Applicants argue that Kuna does not teach administration of MIG, and does not teach administration of eosinophils, and therefore does not anticipate the claims of the instant invention.

These arguments have been fully considered and are persuasive in light of the Applicants' election on 11/21/2005, without traverse, of the claims of Group I, drawn to administration of MIG to inhibit eosinophil recruitment or function, as set forth in the requirement for restriction mailed on 10/19/2005. Therefore, although Kuna does teach administration of IP-10, Kuna is silent regarding administration of MIG and thus does not anticipate the *elected* invention.

New Grounds of Rejection

2. Claims 1, 6 and 7 are rejected under 35 U.S.C. 102(b) as being anticipated by Jinquan *et al* ("Jinquan" - *J. Immunol.* 2000, Vol. 165, p. 1548-1556 – cited in the IDS received on 5/10/2004). The claims are drawn to a method of inhibiting eosinophil recruitment or eosinophil function, specifically receptor internalization, by administration of a pharmaceutical composition comprising MIG.

Jinquan teaches administration of MIG to eosinophils (see p. 1550 and Fig. 1). Jinaquan does not teach administration to a subject; however, the claims of the instant invention read on both in vivo administration, and *in vitro* administration of MIG to eosinophils. Although Jinquan does not specifically recite inhibition of eosinophil recruitment or inhibition of receptor internalization, it would be expected, in the absence of evidence to the contrary, that the administration MIG to eosinophils taught by Jinquan would necessarily result in inhibition of at least one of these activities. Furthermore, it would also be expected that the administration of MIG to eosinophils taught by Jinquan would necessarily result in some perturbation, to some degree, of a signal transduction kinase function, and specifically, would perturb, so some degree, Erk1 or Erk2. Because the USPTO does not have the facilities for testing the MIG and eosinophils of Jinquan, the burden is on the Applicants to show a novel and unobvious difference between the claimed method and that of the prior art. See In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and Ex parte Gray, 10 USPQ 2d 1922 1923 (PTO Bd. Pat. App. & Int.). Therefore, Jinquan mets the limitations of claims 1 and 6-7 of the instant application.

3. Claims 1, 6 and 7 are rejected under 35 U.S.C. 102(b) as being anticipated by Loetscher *et al* ("Loetscher" - *J. Biol. Cheml.* 2001, Vol. 276, p. 2986-2991 – cited in the previous action mailed on 1/31/2006). The claims are drawn to a method of inhibiting eosinophil recruitment or eosinophil function, specifically receptor internalization, by administration of a pharmaceutical composition comprising MIG.

Loetscher teaches administration of MIG to eosinophils, and shows that MIG inhibits eosinophil chemotaxis in response to eotaxin (see Fig. 1, part D). Because the claims can be interpreted as reading on in vitro methods of administration of MIG to eosinophils, Loetscher thus meets the limitations of claim 1. Furthermore, although Loetscher does not specifically recite perturbation of any signal transduction kinase function in response to MIG administration, it is noted that Loetscher teaches that Ca^{2+} mobilization in response to eotaxin in inhibited by MIG administration (see abstract), thereby showing that signal transduction events are inhibited by MIG administration. It would be expected therefore, in the absence of evidence to the contrary, that MIG administration to eosinophils would inherently "perturb" to some degree a signal transduction kinase function such as Erk1 or Erk2 activity. Because the USPTO does not have the facilities for testing the MIG and eosinophils of Loetscher, the burden is on the Applicants to show a novel and unobvious difference between the claimed method and that of the prior art. See In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and Ex parte Gray, 10 USPQ 2d 1922

1923 (PTO Bd. Pat. App. & Int.). Therefore, Loetscher also meets the limitations of claims 6-7 of the claimed invention.

4. Claims 1, 3, 6-7, 14, 16, 19, 21, 24, 27, 44-45, and 47-49 are rejected under 35 U.S.C. 102(b) as being anticipated by Streiter *et al* (US 5,871,723). The claims are drawn to methods of treatment, wherein said methods comprise administration of a pharmaceutical composition comprising MIG.

Streiter *et al* teaches methods of treatment comprising administration of compositions comprising MIG to mammalian subjects, including humans (see claims 1, 3, 17, and 20; see also Examples XIII and XIV). It is noted that independent claims 1, 14, 24, 27, and 44 do not recite a specific patient population to be treated, and thus read on administration of MIG to any subject or patient population. It is also noted that claim 21 recites a patient exposed to an allergen, which reads on a large segment of the population, if not all of the population, because subjects are continually exposed to allergens such as dust, pollen, etc, every day. Because the subjects/patients of Streiter *et al* would be expected to have eosinophils and be exposed to an allergen such as dust or pollen, and the method of MIG administration taught by Streiter *et al* would result in said eosinophils being exposed to the administered MIG, the methods of Streiter et al meet the limitations of these claims. Streiter *et al* also teaches administration by various methods, including parenteral and other routes that would result in systemic administration (column 14, lines 39-40), and thus meets the limitations of claim 19 regarding systemic administration. Furthermore, although Streiter *et al* does not explicitly disclose that the administered MIG has eosinophil inhibiting activity, it would be expected, in the absence of evidence to the contrary, that MIG administered by the methods of Streiter *et al* would inhibit eosinophil recruitment or function, including receptor internalization, Erk 1/Erk 2 perturbation, and would inhibit eosinophil responses to a Th2 cytokine or eotaxin, or negatively regulate an inflammatory cell with a lung of said subject/patient. Because the USPTO does not have the facilities for testing the method of Streiter *et al*, the burden is on the Applicants to show a novel and unobvious difference between the claimed method and that of the prior art. See In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and Ex parte Gray, 10 USPQ 2d 1922 1923 (PTO Bd. Pat. App. & Int.).

Therefore, because Streiter *et al* discloses methods of administering MIG which would be expected to meet the functional limitations of the claims, Streiter *et al* meets the limitations of claims 1, 6-7, 14, 16, 19, 24, 27, 44-45, and 46-48 of the instant application. Furthermore, because the metes and bounds of "eosinophil associated disease" are not defined, as set forth above, and any disease in which eosinophils are present can be considered an "eosinophil associated disease", the methods of Streiter *et al* also meet the limitations of claim 49. Finally, Streiter *et al* teaches administration of MIG comprising an

ELR substitution (see Example XVI), which can be considered a peptide "derived" from MIG, and thus meets the limitations of claim 3.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Rejections maintained/New grounds of rejection

1. Claims 1, 3, 5, 14, 16-21, 23-29, 31-33, 44-45, and 46-49 *remain rejected*, and claims 6-7 and 9-11 are also rejected under 35 USC § 103(a) as being obvious in view of the combination of Kuna *et al* ("Kuna" – WO 94/21277), Loetscher *et al* ("Loetscher" – *J. Biol. Chem.*, 2001, Vol. 276, p. 2986-2991), and Kaplan (*Int. Arch. Allergy Immunol.*, 2001, Vol. 124, p. 423-431), as set forth on pages 11-13 of the office action mailed on 1/31/2006.

The subject matter of the claims of the instant invention is discussed above. Kuna discloses methods of treating allergic disease in mammals such as humans, wherein said methods comprise administering chemokines such as RANTES, MIP-1α, MIP-1β, CTAP-III, or IP-10. Kuna also teaches treatment of diseases such as asthma by administration of chemokines by various routes, including inhalation of an aerosol, and teaches dose ranges of 0.5 to 500 μg/kg , and preferably 20 to 200 μg/kg. Kuna is silent regarding administration of MIG.

Loetscher teaches that MIG competes with eotaxin for binding to the eotaxin receptor, CCR3, and inhibits eotaxin-mediated cell migration and intracellular Ca^{2+} flux. Loetscher also teaches that eotaxin is expressed by eosinophils and is involved in basal and inflammation-dependent traffic of eosinophils, and furthermore, neutralization of eotaxin results in reduced eosinophil infiltration and airway inflammation.

Kaplan discloses that eotaxin is required for eosinophil chemotaxis, and is associated with accumulation of eosinophils in allergic responses.

In the response received on 4/28/2006, the Applicants argue that the claims of the instant invention are not obvious in view of Kuna, Loetscher, and Kaplan because Kuna does not disclose administration of MIG, or administration of any chemokine to eosinophils, and thus does not teach or suggest methods of administering MIG to eosinophils. Furthermore, the Applicants assert that the

inhibition of CCR3 by MIG, as taught by Loetscher, results from a different mechanism than that of the instant application. Specifically, the Applicants argue that Loetscher teaches that MIG is a competitive antagonist of CCR3, whereas the instant specification describes MIG inhibition of CCR3 that is not the result of competitive antagonism. Finally, the Applicants argue that Kaplan is a review article that does not cure the deficiencies of Kuna and Loetscher.

These arguments have been fully considered and are not persuasive. A person of ordinary skill in the art, at the time the instant invention was filed, would have been motivated to administer MIG to a subject with inflammatory or allergic conditions such as asthma, by following the combined teachings of Kuna, Loetscher, and Kaplan. The motivation to do so comes from the disclosures of Kaplan and Loetscher, which teach the importance of eotaxin-mediated eosinophil chemotaxis and infiltration in inflammatory and allergic responses, and a molecule, MIG, which inhibits exotaxin-mediated cell migration and signaling. Thus, the disclosures of Kaplan and Loetscher provide the motivation to inhibit eotaxin-mediated eosinophil migration and subsequent eosinophilia by administration of MIG. Kuna, which also teaches treatment of allergic/inflammatory diseases such as asthma by administration of a chemokine, IP-10, which is functionally similar to MIG, provides the motivation to treat asthma by chemokine administration, and provides motivation for administration by aerosol inhalation, as well as specific dose ranges for administration.

Regarding the Applicants arguments that Loetscher discloses inhibition of CCR3 by a mechanism that is different from that of the instant invention, it is noted that the instant claims do not place any limitations on any mechanism by which MIG may inhibit eosinophil activity. Furthermore, regardless of the mechanism through which MIG inhibits eotaxin/CCR3-mediated activity, Loetscher teaches that MIG inhibits eotaxin activity, and thus provides the motivation to inhibit eotaxin by administration of MIG.

Finally, although the cited combination of references does not specifically teach perturbation of a signal transduction kinsase function, or perturbation of Erk1 or Erk2, by administration of MIG, it is noted that the ability to affect these limitations would be a property of MIG, and it would be expected, in the absence of evidence to the contrary, that the method of administering MIG for the treatment of inflammatory/allergic diseases such as asthma, which is obvious in view of Kuna, Loetscher, and Kaplan, would necessarily result in some level of perturbation of some signal transduction kinase function, or some level of perturbation of Erk 1 or Erk 2.

2. Claim 34 *remains rejected* under 35 USC § 103(a) as being obvious in view of the combination of Kuna *et al* ("Kuna" – WO 94/21277), Loetscher *et al* ("Loetscher" – *J. Biol. Chem.*, 2001,

Vol. 276, p. 2986-2991), and Schmid-Grendelmeier *et al* (*J. Immunol.*, 2000, Vol. 169, p. 1021-1027), as set forth on pages 15-17 of the office action mailed on 1/31/2006.

Claim 34 is drawn to a method of alleviating asthma in a patient, wherein said method comprises administering MIG to said patient and thereby inhibiting an IL-13-associated asthmatic response in the patient.

The teachings of Kuna and Loetscher are discussed above. Schmid-Grendelmeirer discloses that IL-13 is an important effector cytokine in allergic diseases such as asthma, and eosinophils from asthmatic patients express IL-13 in response to eotaxin-stimulation.

In the response received on 4/28/2006, the Applicants argue that claim 34 is not obvious in view of Kuna, Loetscher, and Schmid-Grendelmeier because MIG is not a simple competitive antagonist of eotaxin, and none of Kuna, Loetscher, or Schmid-Grendelmeier teach or suggest the effects of MIG on an IL-13 response.

These arguments have been fully considered and are not persuasive. A person of ordinary skill in the art, at the time the instant application was filed, would know that MIG inhibits eotaxin responses (via Loetscher), and that eotaxin-induced IL-13 plays an important role in mediating allergic diseases such as asthma. Therefore, regardless of the mechanism by which MIG inhibits eotaxin, the combination of Kuna, Loetscher, and Schmid-Grendmeier provides the motivation to administer MIG to inhibit CCR3/eotaxin-mediated events, which would necessarily inhibit IL-13 activity in an asthmatic patient.

3. Claim 1 *remains rejected*, and claims 5-7, 9-10, 14, 16-21, 24, 27, 29, 31, 44, and 46-49 are also rejected under 35 USC § 103(a) as being obvious in view of Loetscher *et al* ("Loetscher" – *J. Biol. Chem.*, 2001, Vol. 276, p. 2986-2991), as set forth on pages 17-18 of the office action mailed on 1/31/2006.

The subject matter of the claims of the instant invention and the teachings of Loetscher are discussed above. In the response received on 4/28/2006, the Applicants argue that one of ordinary skill in the art, based on the teachings of Loetscher, would be taught that MIG competing with endogenous eotaxin would result in increased chances that a ligand (eotaxin, MIG, IP-10) would bind to the CCR3 receptor, and would thus expect an increase in receptor internalization when MIG is administered. However, the Applicants' claim 1 recites a method wherein MIG administration inhibits eosinophil internalization, and therefore Loetscher teaches away from the claimed invention.

These arguments have been fully considered and are not persuasive. As discussed above, Loetscher teaches that MIG competes with eotaxin for binding to the eotaxin receptor, CCR3, and inhibits

eotaxin-mediated cell migration and intracellular Ca^{2+} flux. As currently amended, claim 1 recites a method of inhibiting at least one of eosinophil recruitment or eosinophil receptor internalization, and as set forth above in the rejection under 35 USC 102(b), Loetscher anticipates an *in vitro* method of inhibiting eosinophil recruitment by administration of MIG. Therefore, it would be obvious to one of ordinary skill in the art, based on the teachings of Loetscher, which also discloses a role for eotaxin in basal and inflammation-dependent traffic of eosinophils, and eosinophil infiltration and airway inflammation, to practice an *in vivo* method of inhibiting eosinophils in allergic or inflammatory conditions by administration of MIG. Regarding the Applicants' arguments, it is noted that Loetscher does not teach away from the Applicants' claimed invention because (1) Loetscher teaches inhibition of eosinophil recruitment by administering MIG, and (2) Loetscher shows that CCR3 receptor internalization is not increased by administration of MIG (see Fig. 8, part A). It is also noted that, in the absence of evidence to the contrary, the method of administration of MIG to a subject, as is obvious in view of Loetscher, would necessarily result in some level of perturbation of a signal transduction kinase function such as Erk1 or Erk 2.

Furthermore, because Loetscher provides the motivation to practice an in vivo administration of MIG for inhibition of eosinophil recruitment, claims 14, 24, 27, and 44 are also obvious in view of Loetscher because no specific patient population is claimed. Thus, based on the teachings of Loetscher it would be obvious to administer MIG to patients to inhibit eosinophil recruitment or chemoattraction, or to inhibit an eosinophil response to a chemoattractant such as eotaxin. Furthermore, it would also be obvious to administer MIG to individuals with eosinophilia or hypereosinophilia because Loetscher teaches that MIG can inhibit recruitment of eosinophils. Although Loetscher does not specifically teach dosages to administer to a patient, or preferred routes of administration, it would be obvious to one of ordinary skill in the art to optimize these variable. MPEP 2144.05 states:

> "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." *In re Aller*, 220 F.2d 454, 454, 105 USPQ 223, 235, (CCPA 1955).

In the instant case, Loetscher teaches the general conditions of MIG administration for inhibition of eosinophil recruitment and function, and therefore it would be obvious to optimize variables such as dosage and route of administration in order to practice a method of administering MIG to a patient for the purpose of inhibiting eosinophil recruitment or treating a patient with eosinophilia or other "eosinophil-associated diseases", and thus claims 9-10, 16-20, 28, 31, and 47-49 are also obvious in view of Loetscher.

Rejections withdrawn

4. Rejection of claims 6-7 under 35 USC § 103(a) as being obvious in view of the combination of Kuna *et al* ("Kuna" – WO 94/21277), Loetscher *et al* ("Loetscher" – *J. Biol. Chem.*, 2001, Vol. 276, p. 2986-2991), and Bates et al ("Bates" – J. Biol. Chem., 2000, Vol. 10968-10975), as set forth on pages 14-15 of the office action mailed on 1/31/2006, is *withdrawn*.

In the response received on 4/28/2006, the Applicants argue that Bates does not teach or suggest the ability of any factor other than IL-5 to affect Erk1/Erk2 phosphorylation, and therefore the claims are not obvious in view of any combination based on Bates.

These arguments have been fully considered and are persuasive because Bates is silent regarding Erk1/Erk2 phorphorylation in response to MIG stimulation. Furthermore, this rejection is being withdrawn in favor of the new grounds of rejection of claims 6-7 under 35 USC 102(b) as being anticipated by Loetscher (see 35 USC 102(b) rejection #3 above), as well as the new grounds of rejection under 35 USC 103, as being obvious in view of Kuna, Loetscher, and Kaplan (see 35 USC 103 rejection #1 above).

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1, 3, 5-7, 9-11, 13-14, 16-21, 23-29, 31-34, 44-45, and 47-49 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim 1 of copending Application No. 11/091,288. Although the conflicting claims are not identical, they are not patentably distinct from each other.

The subject matter of the claims of the instant invention is discussed above. Claim 1 of the '288 application is drawn to a method of reducing at least one of eosinophil recruitment or eosinophil signaling, wherein said method comprises administering a pharmaceutical composition comprising MIG to an eosinophil. Because claim 1 of the '288 application reads on both *in vitro* and *in vivo* methods, the claim can be interpreted as an in vivo method of administering MIG for inhibition of eosinophil function. Thus, one of ordinary skill in the art, in practicing the invention of the '288 application, would find it obvious to administer MIG to subjects in need of inhibition of eosinophil function, as claimed in the instant application. Furthermore, although the '288 application does not recite treatment of diseases such as asthma or eosinophilia, it would be obvious to one of ordinary skill in the art to treat these eosinophil-mediated diseases by the method of claim 1 of the '288 application, and it would also be obvious to a skilled artisan to optimize such parameters as dosage and route of administration. Therefore, the subject matter of the '288 application and that of the instant application are not distinct from each other.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Conclusion

No claim is allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bruce D. Hissong, Ph.D., whose telephone number is (571) 272-3324. The examiner can normally be reached M-F from 8:30 am - 5:00 pm. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Nickol, Ph.D., can be reached at (571) 272-0835. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Bruce D. Hissong
Art Unit 1646

/Robert S. Landsman/
Primary Examiner, Art Unit 1647